## REMARKS

This is in response to the previous Office Action mailed on November 20, 2003. Due to an omission of the phrase "specific and substantial" from the introductory paragraph of the rejection for credible asserted utility or a well-established utility, the Examiner has made the previous Office Action non-final.

**Rejection under 35 USC §101:**

At page 3 of the Office Action, the Examiner has rejected claims 4, 8, 9, and 24-29 under 35 U.S.C.§101. In summary, the Examiner has stated that the claimed isolated nucleic acid molecules are not supported by either a specific and substantial credible asserted utility or a well-established utility and, consequently, the skilled artisan would not know what the protein does.

The Examiner stated that the asserted function of the claimed nucleic acids being a vacuolar ATP synthase based on the structural similarity of the protein comparison with a known vacuolar ATP synthase 16 kDa proteolipid subunit is not credible, because "the degree of similarity is well outside of the similarity found within the family of proteins having the asserted function."

In Applicants' previous response, dated August 15, 2003, Applicants have argued that the claimed isolated nucleic acid molecules, such as SEQ ID NOS:1 and 3, that encode a specified amino acid sequence, SEQ ID NO:2, and methods of making and using such nucleic acid molecules have several uses that meet the requirements of 35 U.S.C.§101 and the first paragraph of 35 U.S.C.§112. These, as well as the accepted state of the art view that such molecules have uses within the commercial marketplace in the drug development cycle, since they encode previously unidentified members of important pharmaceutical targets, establishes the utility of the claimed invention.

Applicants have also provided further support to the functional claim of the present invention. The Hummer search result shows that the protein of the present invention has a statistically significant domain of ATP synthase subunit C. Homology search results reveal that the present invention has 52% homology with a tomato vacuolar protontranslocating ATPase. Hence, the domain of the ATPase of the present invention is highly conserved even at the low homology, in contrast to the Examiner's assertion.

In response to Applicant's arguments, the Examiner argues that the evidence of record does not support Applicant's contention that the claimed invention encodes a vacuolar ATP synthase subunit. The Examiner points out that "polypeptide having the function of a vacuolar ATP synthase subunit have a high degree of structural conservation, and even an insect vacuolar ATP synthase subunit C is more closely related to the human vacuolar ATP synthase than is the polypeptide encoded by the instant claimed nucleic acid, which is also of human origin." The Examiner further argues that while many proteins are known to comprise ATPase domains, the vast majority of them do not have vacuolar ATP synthase function and therefore the functional domains comprised by the protein encoded by the claimed nucleic acid are generic to proteins having widely divergent function and the asserted vacuolar ATP synthase function is not supported.

Additionally, the Examiner argues that the disclosure fails to teach the skilled artisan what real world problem will be addressed. The specification does not provide a single example of a disease than can be treated using the claimed invention or molecules that interact with polypeptide encoded. The Examiner argues that the specification teaching that molecules will be used to diagnose or treat transporter-related conditions specific to the subfamily of transporters is not a specific and substantial utility but instead an "invitation to the skilled artisan to discover for himself 'transporter-related conditions that are specific for the subfamily of transporters that are one of the present invention belongs to', and then devise a diagnostic or therapeutic approach to that condition. Examiner states that "Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' utility are not substantial utilities." The Examiner reiterates his argument from the last Office action, stating that it is not useful to probe for related nucleic acid molecules or expression levels unless some functional meaning can be attributed to the relatedness or expression of the identified nucleic acid molecules. The Examiner further argues that results from a diagnostic assay are not useful if the findings cannot be correlated with a pathological state.

Applicants respectfully traverse this rejection based on the following remarks.

While an insect vacuolar ATP synthase subunit C may be more closely related to the human vacuolar ATP synthase than the instant polypeptide, it is unclear to Applicants how this relationship brings into question the identification of the instant polypeptide as a vacuolar ATP synthase. Clearly the instant polypeptide also shares significant sequence identity with other

vacuolar ATP synthase subunits (page 5 of the Office action dated February 24, 2003). The Examiner appears to be basing the rejection upon the assumption that the instant polypeptide should be closer in sequence identity to a human vacuolar ATP synthase subunit than that from another species. The Examiner has not provided any evidence or teaching supporting this assumption and that would contradict Applicants' assertion that the instant polypeptide is indeed a vacuolar ATP synthase subunit.

That many proteins are known to comprise ATPase domains and the vast majority of them do not have vacuolar ATP synthase function is not disputed. However, Applicants point out that the Hummer search result shows that the protein of the present invention has a statistically significant domain of ATP synthase subunit C, not just an ATPase domain. The homology search reveals that the present invention has 52% homology with tomato vacuolar protontranslocating ATPase, again supporting that even at this low homology, the ***vacuolar ATP synthase*** domain is highly conserved. Therefore, the evidence as a whole supports the instant polypeptide as a vacuolar ATP synthase.

With regard to the failure to teach what real world problem will be addressed, Applicants point out that the instant polypeptide is a vacuolar ATP synthase and as such, the teachings disclosed in the specification on uses for the claimed nucleic acid and polypeptide molecules are specific and substantial. A skilled artisan would recognize the importance of a vacuolar ATP synthase, which is well known in the art, and how the specification teachings address a real world problem.

The specification teaches that the differential regulation of H+-K+-ATPases (HKAs) takes place at the molecular level in acid-base and electrolyte disorders. The specification further teaches that functional and molecular studies indicate the presence of both transporters in the kidney, which are presumed to mediate the exchange of intracellular H+ for extracellular K+. To date there are no data to indicate that the colonic HKA (HKAc) plays a role in H+ secretion or K+ reabsorption under normal conditions. However, HKAc shows adaptive regulation in pathophysiological conditions such as K+ depletion, NaCl deficiency, and proximal renal tubular acidosis, suggesting an important role for this exchanger in potassium, HCO3, and sodium (or chloride) reabsorption in disease states such as polycystic kidney disease (see pages 13 and 14). Moreover, as vacuolar ATP synthases are known in the art and function in cellular and physiological processes (Martinez-Zaguilan et al. (Am. J. Physiol. Cell Physiol. Vol. 265, pp.

C1015-C1029, 1993) identify vacuolar ATP synthase in the plasma membrane of human tumor cells; Brown et al. (J. Exp. Biol. Vol. 203, pp. 137-145, 2000) report vacuolar ATP synthase involved in renal acidification; Chatterjee et al. (Proc. Natl. Acad. Sci. USA Vol. 89, pp 6257-6261, 1992) identify osteoclast vacuolar ATP synthase that function in bone resorption) and have been identified in the disclosure as having tissue specific expression patterns, the disclosed utilities do not require or constitute carrying out further research to identify or reasonably confirm a real world utility. The instant polypeptide is a vacuolar ATP synthase and therefore the disclosed utility is substantial.

Applicants have previously argued (Applicants' response dated August 15, 2003) that the utility requirement of a claimed invention requires that an invention must have a specific, substantial and credible utility. These requirements are defined in broad terms in cases such as *Brenner v. Manson,* 148 USPQ 689 (S. Ct. 1966) and the recently adopted Utility Guidelines from the USPTO. The Examiner stated that the present invention failed to disclose any properties of the present invention, SEQ ID NO: 2 that is associated with any disease state. However, such a requirement substantially conflicts with the decision made by the CCPA. It is noted that the prior art teaches vacuolar ATP synthase involved in renal acidification, and the role of vacuolar ATP synthase in osteoclast bone resorption (see Brown et al and Chatterjee et al).

Applicants have argued (Applicants' response dated August 15, 2003) that the CCPA in *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), clearly accepted a showing of less than a specific therapeutic use of a claimed chemical compound as satisfying the utility requirement. Summarizing, Applicants argued that similar to the *Nelson* case, the instant vacuolar ATP synthase of SEQ ID NO: 2 has useful value in the drug discovery process even though the molecule may not be associated with a specific treatment and/or diagnosis of a particular disease.

The Examiner is not persuaded and argues that the facts in *Nelson v. Bowler* are different from those of the instant case. The Examiner argues that the pharmacological activity demonstrated by Nelson was sufficient to satisfy the utility requirement and that no pharmacological activity has been demonstrated in the instant case. The Examiner states that the therapeutic application of any pharmaceutical that acts as a transporter is highly dependent on the particulars of the transporter and that simply knowing that a nucleic acid encodes some form of transporter does not provide the skilled artisan with a specific and substantial utility. The

Examiner concludes by stating that he can "find nothing in the art that would direct the skilled artisan to treatment or diagnosis of a specific condition."

Applicants respectfully traverse this rejection based on the following remarks.

As Applicants have identified the instant polypeptide as a vacuolar ATP synthase subunit, this is not unlike the facts of *Nelson v. Bowler*, where several compounds were identified as belonging to the family of natural prostaglandins. According to *Nelson*, not establishing a specific therapeutic use does not preclude a practical utility. In the instant case, the practical utility or "real world utility" is provided by disclosure of SEQ ID NO: 2 as a vacuolar ATP synthase. Applicants argue that one skilled in the art can use the instant invention in a manner that provides some immediate benefit to the public. Like *Nelson*, which states that "knowledge of the pharmacological activity of any compound is obviously beneficial to the public," the knowledge that the polypeptide of the instant invention is a vacuolar ATP synthase brings benefit to the public.

Applicants have previously argued (Applicants' response dated August 15, 2003) that the utility rejection raised by the Examiner also conflicts with the case *Juicy Whip v. Orange Bang* (Fed. Cir. 1999). Summarizing, the polypeptides and encoding nucleic acid molecules of the present invention are well known in the art to be valuable drug targets and therefore have readily apparent commercial utilities, such as for screening potential drug compounds, producing antibodies, developing hybridization probes and primers, etc.

The Examiner argues that the disclosure must provide a specific and substantial credible utility. The issue for the instant case is not whether the asserted utility is credible but whether a specific or substantial utility has in fact been asserted. The Examiner states that his position is "not that the claimed nucleic acid will never be useful, but that the disclosure fails to teach, in specific and substantial terms, what the claimed nucleic acid is to be used for."

Applicants respectfully traverse this rejection based on the following remarks.

As set forth above, Applicants have identified the instant nucleic acids as encoding a vacuolar ATP synthase. Applicants have provided arguments to support this assertion of a specific and substantial utility.

Applicants have argued previously (Applicants' response dated August 15, 2003) that the disclosure of the function of the transporter is sufficient. Summarizing, novel transporter/nucleic acids are commercially useful for developing therapeutics/diagnostics for these and other

pathologies and that not all nucleic acid molecules, and actually a very limited number, of the 3 billion bases that make up the human genome will encode a protein for these and the other disclosed uses.

The Examiner is not persuaded and points out that even if the claimed invention has utility, the skilled artisan does not know what that utility is and must go discover it for himself.

Applicants respectfully traverse this rejection based on the following remarks.

As set forth above, vacuolar ATP synthases are known in the art and function in cellular and physiological processes (vacuolar ATP synthase involved in renal acidification; osteoclast vacuolar ATP synthase functions in bone resorption) and have been identified in the disclosure as having tissue specific expression patterns, the disclosed utilities do not require or constitute carrying out further research to identify or reasonably confirm a real world utility. The instant polypeptide is a vacuolar ATP synthase and therefore the disclosed utility is specific and substantial.

Applicants have argued previously (Applicants' response dated August 15, 2003) that by placing a new member of the transporter protein family into the public domain through the patenting process, the present invention is not only a clear advancement over the prior art (a newly discovered protein/gene) but also enables significant advancement in medicine and further discovery. The Utility requirement cannot be used to contradict the reasons for the patent system, to encourage early disclosures of inventions so that others can benefit from, improve upon, and further develop such inventions. This is particularly important in medicine, wherein early disclosure of key inventions (such as new transporter proteins and encoding nucleic acid molecules) is needed to facilitate the early development of new therapies and diagnostics to treat illnesses.

The grant of a patent to the claimed isolated nucleic acid molecule and the resultant disclosure of the nucleic acid and protein sequences to the public will certainly shorten the process for medical researchers to discover other novel uses for the present transporter-encoding nucleic acids. One example disclosed in the specification is that the present nucleic acid molecules can be used to produce protein targets for identifying agents that bind to the protein targets and modulate protein function. Such agents can be used to precisely determine which biological and pathological processes the protein is involved in. Furthermore, such agents that bind to a protein target and modulate cell signaling may subsequently be developed and refined

for use in mammalian therapeutic applications. All of this later discovery and refinement will be done using the presently claimed material. These uses are clearly commercial and substantial uses that are specific for a very limited number of proteins/nucleic acid molecules.

The Examiner argues that "the asserted utility appears to be to identify agents that bind to the protein encoded by the invention ..." and that "developing reagents that can be used to investigate the properties of the claimed invention or treat an unspecified disease is neither a specific nor substantial utility."

Applicants respectfully traverse this rejection based on the following remarks.

Since the protein encoded by the instant invention is a vacuolar ATP synthase for the reasons as set forth above, reagents specific for the instant invention would have a specific and substantial utility.

Applicants have argued previously (Applicants' response dated August 15, 2003), in summary, that in addition to serving as targets for developing molecular probes and therapeutic agents, the disclosed uses of the claimed nucleic acid molecules as probes, primers, and chemical intermediates, particularly in biological assays, is sufficient to satisfy the requirements of 35 USC §101 and §112.

The Examiner is not persuaded and argues that the teachings of the specification are broad recitations on what can be done with any nucleic acid. The Examiner argues that the Applicants have disclosed a nucleic acid for which the function is likely unknown. The Examiner further argues that a teaching of specific utility must actually be contemplated by the inventor.

Applicants respectfully traverse this rejection based on the following remarks.

The disclosed uses of the claimed nucleic acid molecules as probes, primers, and chemical intermediates, particularly in biological assays have specific and substantial utility as the polynucleotides of the instant invention encoded a vacuolar ATP synthase subunit. Such probes and primers would be unique to the instant invention and would not be that of any nucleic acid. This specific utility has been contemplated and identified by the inventors and has been argued above.

At page 10 of the Office Action, the Examiner has rejected claims 4, 8, 9, and 24-29 under 35 U.S.C. §112, 1st paragraph. The Examiner has stated that since the claimed invention is not supported by either a specific and substantial credible asserted utility or a well-established utility

for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully traverse this rejection based on the following remarks.

Applicants have provided arguments, as set forth above, that the instant invention is a vacuolar ATP synthase subunit. The claimed invention is supported by a specific and substantial credible asserted utility and therefore one skilled in the art would know clearly how to use the claimed invention.

In view of law and fact, the utility standard interpreted by the USPTO guidelines is too high. The disclosure of activity of the expressed polynucleotide is not required by any statute or case law interpreting the utility requirement of Section 101, and the enablement requirement of Section 112, first paragraph. The commercial value of a gene that encodes a previously unidentified member of the transporter protein family, members of which are well known in the art to be commercially valuable drug targets, should be sufficient to satisfy the utility requirement. Therefore, applicants respectfully request that the Examiner withdraw the rejection.

**New Grounds: Claim Objections**

At page 11 of the Office Action, the Examiner has objected to claim 9 because it is directed to a genetically modified host cell and would encompass a transgenic animal, which is non-elected subject matter.

Applicants have amended claim 9 so that it does not encompass non-elected subject matter.

**Conclusions**

Claims 4, 8-9, and 24-29 are currently pending.

In view of the above remarks and amendments, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the objections and rejections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,

CELERA GENOMICS

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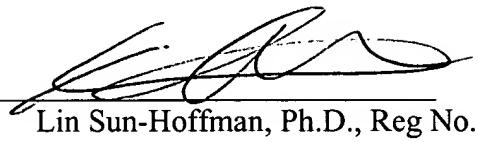
By: 

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